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Testicular Cancer Update

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ABSTRACT

The advances in the treatment of testicular cancer are among the great achievements in modern medicine and these were only possible through the collaborative efforts among cancer researchers around the world. Investigators have been able to address many questions regarding the treatment of patients with disease limited to the testis, metastasis to the retroperitoneum only, and advanced metastatic disease. Questions answered include the chemotherapeutic agents to be used, what combination, the intensity of treatment with appropriate dosing, optimal number of cycles of chemotherapy according to validated risk stratification, appropriate surgical approaches preserving sexual function, treatment of relapsed disease, supportive care measures, and survivorship issues for testicular cancer survivors. Today, cure is achievable in 95% of patients with testicular cancer and in 80% of patients with metastatic disease. Despite remarkable results with frontline and salvage combination chemotherapy, about 10% of patients with metastatic testicular cancer remain incurable and novel treatment approaches are warranted. This review highlights past and recent discoveries in the treatment of patients with testicular cancer.

INTRODUCTION

Testicular cancer is the most common cancer diagnosis in men between 15 and 35 years of age and the incidence has risen during the past several decades.[1] An estimated 8,720 cases of testicular cancer will be diagnosed annually in the United States.[2] The vast majority (95%) of testicular cancer cases are germ cell tumors with other testicular neoplasms occurring rarely (sex cord stromal tumors, lymphoma). Germ cell tumors may also arise in extragonadal locations including the retroperitoneum and the mediastinum.

Substantial advances have been made in the treatment of testicular cancer and these have been among the great achievements in modern medicine. The introduction and refinement of cisplatin-based combination chemotherapy revolutionized the treatment of testicular cancer. Patients diagnosed with testicular cancer who once had dismal prognosis are now curable even in the presence of metastatic disease.[3-6] This disease has become a model for a curable neoplasm and this review will highlight past and present discoveries while emphasizing areas for further investigation.

PATHOGENESIS AND EPIDEMIOLOGY

Germ cell tumors are malignancies of primordial germ cells, these are the cells destined to be become spermatozoa. As neoplastic transformation occurs, these cells develop into various histologies reflecting the broad differentiation capabilities of these cells. The first tumorigenic event leading to the development of germ cell tumors occurs in utero and this leads to the precursor lesion: intratubular germ cell neoplasia.[7,8] In adults, both seminoma and non-seminomatous germ cell tumors are preceded by this premalignant

entity. Intratubular germ cell neoplasia is present in testicular tissue adjacent to germ cell tumors in approximately 90% of adult cases.[9] These premalignant lesions carry a 50% risk of developing testicular cancer within 5 years.[10] Intratubular germ cell neoplasia are derived from gonocytes which have failed to differentiate into spermatogonia and they remain quiescent from the initial insult in utero until hormonal changes occur during puberty.

Testicular germ cell tumors are broadly separated into 2 groups: seminomas and non-seminomas, each constituting about 50% of the cases. These tumors differ in their pathogenesis, histology, clinical course, and response to therapy. Seminomas consist of transformed germ cells that resemble the gonocyte but have a differentiation block. Non-seminomas consist of several histological subtypes including embryonal carcinoma, choriocarcinoma, yolk sac tumor, and teratoma. Embryonal carcinoma cell lines resemble undifferentiated stem cells, and their patterns of gene expression are similar to those of intratubular germ cell neoplasia.[11,12] Choriocarcinoma and yolk sac tumors have extraembryonic differentiation, and teratoma have somatic differentiation.

Several candidate genetic loci have been identified as contributors to the pathogenesis of testicular cancer.[13-15] Germ cell tumors are characterized by the acquisition of extra copies of chromosome 12p. This occurs most commonly through an isochromosome (i12p).[16,17] Chromosome 12q21 contains genes encoding for proteins involved in KITLG–KIT signaling.[18] It has been postulated that the development of intratubular germ-cell neoplasia may involve aberrantly activated KITLG–KIT in utero, which induces arrest of embryonic germ cells at the gonocyte stage; subsequently, overexpression of embryonic transcription factors such as NANOG, sex-determining-region Y–box 17

(SOX17), and octamer-binding transcription factor 3–4 (OCT3/4, also known as POU domain, class 5, transcription factor 1 [POU5F1]) leads to suppression of apoptosis, increased proliferation, and accumulation of mutations in gonocytes.[19]

Single gene mutations are uncommon in testicular cancer. KIT, TP53, KRAS/NRAS, and BRAF are genes most commonly mutated in germ cell tumors and are implicated in their pathogenesis. Different histologic subtypes possess different gene expression profiles that reflect different directions of differentiation.

The distinct gene expression profiles of germ cell tumors is postulated to be achieved through differential epigenetic regulation, in particular DNA methylation.[20] Gonocytes have almost completely demethylated DNA, and this facilitates the accumulation of mutations during cell replication and is implicated in the development of intratubular germ cell neoplasia and germ cell tumors thereafter.

World-wide, there are approximately 72,000 cases and 9,000 deaths per year attributable to testicular cancer.[21] Epidemiologic studies suggest that the incidence of testicular cancer has been rising since the early 1900s.[22-26] Genetic and environmental factors both in utero and during childhood have been proposed to be responsible for this increased incidence. This increase in incidence has been observed only in white males. Testicular cancer is less common in African Americans with the incidence among African Americans estimated to be one-fourth that of whites.[27]

The risk for testicular cancer is increased 8 to 10 fold in the brothers of a person with testicular cancer and 4 to 6 fold in the son of a person with testicular cancer when compared to an unaffected family member.[28] Cryptorchidism occurs in up to 5% of boys

born at term and this is the most well characterized risk factor for testicular cancer.[29] The timing of orchiopexy influences the risk of developing testicular cancer. In a cohort study conducted in Sweden between 1964 and 1999, 16,983 men who were surgically treated for undescended testis were followed for a total of 209,984 person-years. The relative risk of testicular cancer among those who underwent orchiopexy before reaching age 13 was 2.23 compared with 5.4 in those who underwent orchiopexy at age 13 or older. This suggests that hormonal changes around puberty have a role in the development of testicular cancer. Most patients diagnosed with testicular cancer, however, do not have a history of cryptorchidism. A personal history of testicular cancer in the contralateral testis confers an approximately 2% risk for a second primary testicular neoplasm.[30]

CLINICAL PRESENTATION AND DIAGNOSIS

Most patients are diagnosed with testicular cancer when it is still limited to the testes (stage I). The typical presentation is a painless nodule or swelling noted by the patient or his partner. Patients less commonly present with pain in the scrotal area or with gynecomastia. A minority of patients are diagnosed with symptoms related to metastatic disease to the retroperitoneum (stage II) such as back pain or beyond the retroperitoneal lymph nodes (stage III) such as cough, hemoptysis, chest pain, and headaches. Some patients also present with painless supraclavicular lymph nodes.

Scrotal ultrasonography revealing a hypoechoic mass is diagnostic of testicular cancer. A trans-scrotal testicular biopsy should not be attempted given concern for contamination of the scrotum and alteration of the lymphatic drainage of the tumor. Staging for testicular cancer is critical; this should be determined with the use of

computed tomography (CT) of the chest, abdomen, and pelvis and measurement of the levels of tumor markers for germ cell tumors including alpha fetoprotein (AFP) and beta human chorionic gonadotropin (β-hCG). Lactate dehydrogenase (LDH) should only be checked at the first day of initiating chemotherapy as this can be an indicator of the bulk of disease but it is not independently used as a tumor marker or prognostic criterion.

When a patient presents with a suspicious testicular mass that is confirmed on ultrasonography, a radical inguinal orchiectomy is both diagnostic and therapeutic. Pathological interpretation of the tumor sample should include the size, histologic composition (including percentage of each histologic subtype present in the tumor sample), presence or absence of lympho-vascular invasion and rete testis invasion.

STAGE I TESTICULAR CANCER

Seminoma

Patient who present with clinical stage I seminoma are usually cured with orchiectomy alone. Adjuvant radiotherapy was an option for many years but this changed after the introduction of effective chemotherapy. After orchiectomy, options for patients with clinical stage I seminoma include active surveillance, radiation therapy to the para-aortic lymph nodes, or a single dose of carboplatin dosed at an area under the concentration x time curve [AUC] of 7. Most patients today elect for active surveillance given the low chance of disease recurrence. If radiotherapy is the choice, 20 Gy is delivered to the ipsilateral retroperitoneal lymph nodes. If the patient has a history of prior surgery in the inguinal, pelvic, or scrotal areas, then the radiation field is expanded to include the inguinal lymph nodes. The risk for relapse is higher with active surveillance (20%)

versus chemotherapy or radiation therapy (4%) but the long-term survival is approximately 99% irrespective of the initial options chosen by the patient.[31-33] Risk factors for relapse in clinical stage I seminoma include involvement of rete testis or having a primary tumor larger than 4cm.[34] In a Danish population-based study of 1,954 patients there were 369 relapses (19%). Disease specific survival at the median follow-up of 15 years was 99%.[33] At our institution, the surveillance regimen consists of history and physical examination, tumor markers including AFP and hCG, and CT abdomen every 4 months during the first year, every 6 months during the second year, and then annually during the 3rd, 4th, and 5th year of follow-up. If a patient has history of pelvic, inguinal, or other surgery that would alter the lymphatic drainage, then a CT abdomen and pelvis is obtained for surveillance.

Non-seminoma

For patients with stage I non-seminomatous germ cell tumor, options after orchiectomy include active surveillance, nerve-sparing retroperitoneal lymph node dissection, and adjuvant chemotherapy with bleomycin-etoposide-cisplatin (BEP) for 1 cycle. Several studies have indicated that the long-term cure rates with any of these options is 99%.[35-39] Risk factors for relapse in patients with clinical stage I non-seminoma include the presence of lympho-vascular invasion and having embryonal carcinoma as the predominant histology in the primary tumor.[35,40] The risk for relapse in patients with no risk factors is approximately 15% with surveillance; with the presence of risk factors this rate increases to approximately 50% with surveillance. In a large retrospective study of 1,139 patients with clinical stage I non-seminoma, cure rate was 99% in all patients irrespective of their initial risk factors for relapse or choice of treatment after

orchiectomy.[35] Moreover, the vast majority of relapses occurred within 2 years of orchiectomy. The preference at our institution is for active surveillance in nearly all patients who are able to adhere to the close follow-up schedule. We recommend a surveillance program with history and physical examination and tumor markers (AFP and hCG) every 2 months during the first year, every 6 months during the second year, and annually during years 3, 4, and 5. Imaging should include chest radiography and CT abdomen every 4 months during the first year, every 6 months during the second year, and annually during years 3, 4, and 5 of follow-up. If a patient has history of pelvic, inguinal, or other surgery that would alter the lymphatic drainage, then a CT abdomen and pelvis is obtained for surveillance. There are complicated arguments for and against any of the 3 options for the management of clinical stage I testicular cancer. These are illustrated in Table 1.

STAGE II TESTICULAR CANCER

Seminoma

Patients with stage II seminoma have metastatic disease confined to the retroperitoneal lymph nodes. Low volume stage II disease, defined by lymph nodes ≤3cm in diameter, can be treated with 30-36 Gy of radiation to the para-aortic and ipsilateral iliac lymph nodes.[39] In all other patients, the preferred therapy is 3 courses of combination chemotherapy with bleomycin-etoposide-cisplatin (BEP) or 4 courses of etoposide-cisplatin (EP).[41] With cisplatin-based combination chemotherapy, cures are achieved in 98% of patients. Patients who have bulky stage II disease should not undergo radiotherapy as the relapse rate is high with radiotherapy.[42] Post-treatment residual masses can be challenging to interpret in patients with seminoma. These findings

usually represent desmoplastic changes; surgical resection of these residual masses only rarely shows residual seminoma and can be quite challenging. We typically observe patients with post-treatment residual masses < 3cm in diameter. Masses larger than 3cm have a higher likelihood of containing residual viable seminoma. In these cases, a positron-emission tomographic (PET) scan performed 6 weeks after completion of therapy can assist in making the decision whether surgical intervention is needed to resect residual retroperitoneal masses.[43]

A phase II clinical trial is currently evaluating retroperitoneal lymph node dissection as the primary treatment in patients with stage II seminoma and non-bulky disease (ClinicalTrials.gov number, NCT02537548).

Non-seminoma

Patients with low volume stage II non-seminomatous germ cell tumor have metastatic disease confined to the retroperitoneal lymph nodes, lymph node size < 3cm, and normal tumor markers (AFP and hCG) post-orchiectomy. These patients are typically treated with retroperitoneal lymph node dissection.[44] At our institution, patients with high volume stage II disease or increasing levels of tumor markers (AFP or hCG) are treated with chemotherapy consisting of 3 cycles of BEP or 4 cycles of EP. About 95-99% of patients with stage II non-seminoma achieve cures with the above regimens.

Post-chemotherapy, patients who have persistently enlarged retroperitoneal lymph nodes with normal tumor markers (AFP and hCG) should undergo post-chemotherapy retroperitoneal lymph node dissection for resection of residual tumor and/or teratoma. The management of patients with stage II non-seminoma who have complete serologic

and radiographic remission remains unsettled. At our institution, we do not recommend retroperitoneal lymph node dissection if the retroperitoneal lymph nodes have normalized on CT imaging. In a retrospective study, 141 patients with non-seminoma who achieved complete radiographic and serologic remission after first-line chemotherapy were followed for a median of 15.5 years with no post-chemotherapy retroperitoneal lymph node dissection. The 15-year recurrence-free survival was 90% and cancer-specific survival was 97%.[45] Given concern for the presence of viable germ cell tumor and/or teratoma in some patients with normal-sized post-chemotherapy lymph nodes, some investigators recommend post-chemotherapy retroperitoneal lymph node dissection in most patients.[46] In a meta-analysis, 1,043 patients with metastatic non-seminoma treated with cisplatin-based chemotherapy were evaluated and among these 588 underwent post-chemotherapy retroperitoneal lymph node dissection while 455 were followed with surveillance only.[47] In patients who underwent post-chemotherapy resection, the pooled estimates of necrosis, teratoma and active cancer were 71%, 24%, and 4% respectively. Among patients who were followed with post-chemotherapy surveillance only, the pooled estimate of relapse was 5% with a retroperitoneal-only relapse rate of 3%. Therefore, post-chemotherapy retroperitoneal lymph node dissection can be avoided in approximately 95% of patients with radiographic and serologic remission and at our institution these patients are followed with surveillance.

STAGE III TESTICULAR CANCER

The discovery of cisplatin[48] and the refinement of combination chemotherapy revolutionized the treatment of metastatic testicular cancer. In 1974, the addition of

cisplatin to a regimen of vinblastine and bleomycin achieved 5-year survival rate of 64% which was unprecedented compared with previous chemotherapy regimen.[4] Cisplatin-based combination chemotherapy regimens were then refined in multiple subsequent studies.[3,5,6] Based on a randomized clinical trial showing improved efficacy and less toxicity, first-line chemotherapy with 4 cycles of bleomycin-etoposide-cisplatin (BEP) became the standard of care for patients with advanced testicular cancer.[6] Investigators recognized that each additional cycle of chemotherapy caused cumulative toxicity, hence randomized trials in patients with low-risk disease showed that 3 cycles of BEP had similar outcomes and were non-inferior to BEP x 4 or BEP x 3 plus etoposide-cisplatin (EP) x 1.[5,49] A randomized clinical trial comparing 3 cycles of BEP and 4 cycles of EP in patients with low-risk disease favored BEPx3 (4-year event-free survival rate of 91% vs. 86%) although the difference was not statistically significant (P=0.14).[50] For patients with low-risk metastatic disease, our preferred regimen is 3 cycles of BEP but 4 cycles of EP is also considered a standard regimen. Randomized trials have shown numerical superiority of BEPx3 over EPx4 although this was not statistically significant.

After a multinational analysis in 1997, the International Germ-Cell Cancer Collaborative Group (IGCCCG) published a consensus statement classifying patients with metastatic GCT into good, intermediate, and poor risk disease based on specified prognostic criteria: primary tumor site, metastatic sites, and the amplitude of serum tumor marker levels.[51] This classification was based on an international collaboration evaluating 5,202 patients with metastatic germ cell tumors. For seminoma: good risk patients were defined as having any primary tumor site, no non-pulmonary visceral metastasis (liver, brain, bone, or other), and any tumor marker levels (hCG, LDH; AFP by definition is

normal in patients with seminoma); intermediate risk patients were defined as having non-pulmonary visceral metastasis. For non-seminoma: good risk patients were defined as having primary testis or retroperitoneal tumor site and no non-pulmonary visceral metastasis and good tumor marker levels (AFP < 1,000 ng/mL, hCG < 5,000 mIu/mL, LDH < 1.5 x upper limit of normal); intermediate risk patients were defined as having intermediate tumor marker levels (AFP 1,000-10,000 ng/mL, hCG 5,000-50,000 mIu/mL, LDH 1.5-10 x upper limit of normal); poor risk patients were defined as having primary mediastinal tumor site, non-pulmonary visceral metastasis, or poor tumor marker levels (AFP > 10,000 ng/mL, hCG > 50,000 mIu/mL, LDH > 10 x upper limit of normal).[51] Good risk germ cell tumors represented 60% of all metastatic cases with a 5-year progression-free survival (PFS) of 88% and a 5-year overall survival (OS) of 91%. Intermediate risk germ cell tumors represented 26% of all cases with a 5-year PFS of 75% and a 5-year OS of 79%. The poor risk category represented 14% of patients with a 5-year PFS of 41% and a 5-year OS of 48%.

Using the above risk stratification, the treatment of metastatic testicular cancer has been refined according to the patient's chance for response to first-line chemotherapy and risk for relapse. Patients with good risk disease are treated with 3 cycles of BEP and 4 cycles of EP and are expected to have > 90% cure rate with first-line chemotherapy.[3,5,6,49,50] Patients with intermediate risk disease are treated with 4 cycles of BEP or 4 cycles of etoposide, ifosfamide, cisplatin (VIP) and are expected to achieve > 80% cure rate with first-line chemotherapy.[52-54] Patients with poor risk disease are treated with 4 cycles of BEP or VIP and are expected to achieve a cure rate of 50-60% with first-line chemotherapy.[53,55-59]

The intermediate risk group constitutes a heterogeneous category with varying outcomes. At our institution, we consider that 4 cycles of BEP or VIP might be an overtreatment in some patients with intermediate risk disease and we recommend treatment with 3 cycles of BEP followed by 1 cycle of EP in these select patients. A retrospective analysis did not show any difference in survival outcomes among intermediate risk patients who received treatment with either of these regimens.[60]

Several attempts have been made to intensify first-line therapy with hopes of increasing cure rates among patients with intermediate or poor risk disease. Unfortunately, these attempts have failed at showing any survival advantage over 4 cycles of BEP or VIP and these intensified regimens had more toxicity in clinical trials.[52,55-57] Some investigators proposed intensification of therapy according to the rate of decline of tumor markers (AFP and hCG) in patients with high risk disease after the first or second cycle of BEP chemotherapy.[58] This strategy resulted in fewer relapses and appeared to improve overall survival, albeit at the expense of more toxicity, compared to the control arm on this study but not compared to contemporary survival outcomes.[59,61]

A novel regimen of paclitaxel-ifosfamide-cisplatin (TIP) has been studied in phase II trial enrolling patients with intermediate and poor risk germ cell tumors. Results showed a complete response rate of 68% and a partial response rate of 13%.[62] With this regimen the estimated 3-year PFS and OS for intermediate risk patients was 90% and 100%, and for poor risk patients was 63% and 87% respectively. A randomized phase II trial comparing BEP vs. TIP as first-line therapy for patients with intermediate and poor risk germ cell tumors is ongoing (ClinicalTrials.gov number, NCT01873326).

RELAPSED TESTICULAR CANCER

The most effective salvage regimen for patients with relapsed testicular cancer remains unsettled. Patients who relapse after initial chemotherapy, with anatomically confined disease, can still be cured by salvage surgery.[63] The vast majority of patients, however, will be treated with salvage chemotherapy including standard-dose chemotherapy or high-dose chemotherapy. Second-line standard-dose chemotherapy options include etoposide-ifosfamide-cisplatin (VIP), vinblastine-ifosfamide-cisplatin (VeIP), or paclitaxel-ifosfamide-cisplatin (TIP).[64-66]

High-dose chemotherapy followed by bone marrow transplant was first investigated at Indiana University in 1986.[67] Bone marrow transplantation was replaced by peripheral-blood stem cells in 1996. This allowed for more rapid engraftment and hence fewer delays in delivering a second course of high-dose chemotherapy. Among the first 184 patients treated with high-dose chemotherapy and peripheral-blood stem-cell transplant for germ cell tumors that progressed after first-line or second-line cisplatin-based chemotherapy, cures were achieved in 70% of patients in the second-line setting and in 45% of patients who were treated in the third-line or subsequent setting.[68]

In an updated analysis from Indiana University, 364 consecutive patients with relapsed germ cell tumors were treated with high-dose chemotherapy and autologous peripheral-blood stem-cell transplant between 2004 and 2014.[69] With a median follow-up of 3.3 years, the 2-year progression-free survival was 60% and the 2-year overall survival was 66%. Three hundred three patients received high-dose chemotherapy as second-line therapy with a 2-year progression-free survival of 63% and 61 patients received high-dose chemotherapy as third-line or later therapy with a 2-year progression-free survival of 49%. There were 122 patients with platinum refractory disease, defined as

tumor progression within 4 weeks of platinum-based chemotherapy, with a 2-year progression-free survival of 33%. There were 90 patients with seminoma on this study with a 2-year progression-free survival of 90%. Treatment-related death rate was 2.5%.

Investigators at Memorial Sloan Kettering Cancer Center (MSKCC) pioneered another widely used high-dose chemotherapy regimen, which incorporates paclitaxel and ifosfamide as induction chemotherapy and stem-cell mobilization followed by high-dose carboplatin and etoposide with peripheral-blood stem-cell transplant for three cycles (TI-CE regimen).[70] In a phase I/II trial that enrolled 107 patients, the reported 5-year disease-free survival was 47%and overall survival was 52%. Patients who had a satisfactory decline in the tumor marker levels during high-dose chemotherapy had superior progression-free and overall survival; however, even patients with unsatisfactory decline in tumor marker levels could be cured.[71]

The choice of initial salvage chemotherapy for relapsed testicular cancer remains controversial. One of the challenges is determining which patients should be treated with salvage standard-dose chemotherapy versus high-dose chemotherapy. A randomized phase III study comparing sequential with a single course of high-dose chemotherapy showed superior overall survival in the arm receiving sequential high-dose chemotherapy.[72] A prospective phase III trial did not show a difference in survival when comparing etoposide-ifosfamide-cisplatin (VIP) for four cycles versus VIP for three cycles followed by high-dose chemotherapy with carboplatin and etoposide plus cyclophosphamide for one cycle.[73] In 2011, Lorch et al reported outcomes from a large multi-institutional database evaluating 1,594 patients with relapsed germ cell tumors.[74] This retrospective study included a diverse patient population stratified to prognostic

subgroups according to the International Prognostic Factors Study Group. Patients were treated with heterogeneous salvage chemotherapy regimens between 1990 and 2008. In this study, high-dose chemotherapy achieved superior outcomes compared with standard-dose chemotherapy and there was an overall 56% decrease in the risk of progression after first salvage treatment, favoring high-dose chemotherapy. This translated into statistically significant improvement in overall survival with high-dose chemotherapy in all prognostic subgroups except the low-risk group. The superior outcomes with high-dose chemotherapy were more pronounced in patients with intermediate, high, or very high risk disease.

Studies have indicated that patients with high-risk relapsed disease (example: platinum refractory, primary mediastinal non-seminoma, and patients with progressive brain metastases) can be cured with high-dose chemotherapy.[69,70] These results are rarely seen with standard-dose chemotherapy in these high risk patients. With high-dose chemotherapy, cure rates for patients with relapsed primary mediastinal non-seminoma are approximately 25%, for patients with progressive brain metastases approximately 40%, and for patients with platinum refractory disease approximately 33%.[69]

Some investigators advocate the use of high-dose chemotherapy in most patients as the second-line regimen, whereas others have proposed the use of high-dose chemotherapy only in high-risk patients, those who have had a relapse after receiving ifosfamide-based chemotherapy, or those who have had a relapse after two lines of standard salvage therapy. Optimal patient selection for high-dose chemotherapy versus standard-dose chemotherapy as initial salvage is currently being studied in a randomized phase III trial as part of an international collaboration (ClinicalTrials.gov

identifier, NCT02375204). This trial (TIGER, or a Randomized Phase III Trial of Initial Salvage Chemotherapy for Patients with Germ-Cell Tumors) randomizes patients to receive paclitaxel-ifosfamide-cisplatin (TIP) for 4 cycles or ifosfamide plus paclitaxel followed by high-dose carboplatin and etoposide for 3 cycles.

NOVEL APPROACHES IN TESTICULAR CANCER

Although most patients with metastatic testicular cancer will be cured, about 10% of patients have platinum refractory disease and remain incurable. Further advances evaluating the biology of this disease and investigating the mechanism of resistance to treatment is desperately needed. In the era of targeted therapy and immunotherapy, cytotoxic chemotherapy remains the mainstay of treatment for metastatic disease. Unfortunately, early studies with molecularly targeted therapies such as imatinib, sunitinib, thalidomide, and trastuzumab have yielded negative results.[75-78] Studies evaluating the activity of immune checkpoint inhibitors are underway and results will be reported in the near future.[79] Some investigators are evaluating hypomethylating agents as means to overcome the mechanism of resistance to platinum chemotherapy in patients with relapsed refractory germ cell tumors with early phase clinical trials ongoing (ClinicalTrials.gov number, NCT02429466). Other investigators have evaluated the genomic profile of platinum refractory germ cell tumors.[80,81] Unfortunately, consistent targetable genomic alterations have not been identified to date.

SURVIVORSHIP ISSUES IN TESTICULAR CANCER SURVIVORS

Since most patients with testicular cancer will be cured of their disease, this young population of survivors has been considered as a model to evaluate long-term toxic effects of diagnostic and therapeutic interventions.

There is an emerging concern regarding the risk of secondary cancers due to exposure to diagnostic radiation in young patients with testicular cancer undergoing surveillance. A report of 2,569 patients observed for a median of 11 years showed no increased risk of secondary cancer in this group, although follow-up might not have been long enough to detect this risk.[82]

The risk of secondary cancer from surgery, chemotherapy, and radiation therapy has been studied.[83,84] Fung et al evaluated 12,691 patients treated with chemotherapy or surgery and reported a 40% increased risk for solid cancers for patients receiving chemotherapy.[85] In testicular cancer survivors, cumulative doses of etoposide have been associated with an increased risk of developing secondary leukemia that typically exhibits a short latency period, a chromosomal translocation (11q23 and 21q22), and rearrangement of the mixed-lineage leukemia gene.[83] The available data on testicular cancer suggest that the risk of secondary leukemia is dose-related, and that the risk of treatment with etoposide totaling more than 2 g is approximately 2% to 3%.[69,86,87]

Testicular cancer survivors are also at risk for multiple late consequences of therapy including metabolic syndrome, cardiovascular disease, hypertension, infertility, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, and psychosocial disorders.[88-93] A multi-institutional study evaluating the genetic predisposition of long-term cisplatin toxicities, identifying single nucleotide polymorphisms associated with

these toxicities, and collecting data regarding various cardiovascular risk factors in testicular cancer survivors is currently underway.

CONCLUSIONS

The modern history of testicular cancer is that of an oncological success story. The advances made in the diagnosis, prognostication, treatment, surgical expertise, and long-term survivorship care have resulted from collaborations among investigators across the globe. Collaborations are aimed at discovery of novel therapies for patients who are not cured by current therapeutic options and researching approaches for reducing the late effects of therapy. It is only with maintaining this collaborative spirit that researchers will hopefully achieve the unified goal of curing every patient with testicular cancer in the future.

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REFERENCES

1. Nigam M, Aschebrook-Kilfoy B, Shikanov S, et al: Increasing incidence of testicular cancer in the United States and Europe between 1992 and 2009. World J Urol 33:623-31, 2015

2. Cancer Facts & Figures. American Cancer Society, 2016

3. Bosl GJ, Geller NL, Bajorin D, et al: A randomized trial of etoposide + cisplatin versus vinblastine + bleomycin + cisplatin + cyclophosphamide + dactinomycin in patients with good-prognosis germ cell tumors. J Clin Oncol 6:1231-8, 1988

4. Einhorn LH, Donohue J: Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 87:293-8, 1977

5. Einhorn LH, Williams SD, Loehrer PJ, et al: Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol 7:387-91, 1989

6. Williams SD, Birch R, Einhorn LH, et al: Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med 316:1435-40, 1987

7. Chieffi P, Chieffi S: Molecular biomarkers as potential targets for therapeutic strategies in human testicular germ cell tumors: an overview. J Cell Physiol 228:1641-6, 2013

8. Rajpert-De Meyts E: Developmental model for the pathogenesis of testicular carcinoma in situ: genetic and environmental aspects. Hum Reprod Update 12:303-23, 2006

9. Dieckmann KP, Skakkebaek NE: Carcinoma in situ of the testis: review of biological and clinical features. Int J Cancer 83:815-22, 1999

10. von der Maase H, Rorth M, Walbom-Jorgensen S, et al: Carcinoma in situ of contralateral testis in patients with testicular germ cell cancer: study of 27 cases in 500 patients. Br Med J (Clin Res Ed) 293:1398-401, 1986

11. Sperger JM, Chen X, Draper JS, et al: Gene expression patterns in human embryonic stem cells and human pluripotent germ cell tumors. Proc Natl Acad Sci U S A 100:13350-5, 2003

12. Almstrup K, Hoei-Hansen CE, Wirkner U, et al: Embryonic stem cell-like features of testicular carcinoma in situ revealed by genome-wide gene expression profiling. Cancer Res 64:4736-43, 2004

13. Kanetsky PA, Mitra N, Vardhanabhuti S, et al: Common variation in KITLG and at 5q31.3 predisposes to testicular germ cell cancer. Nat Genet 41:811-5, 2009

14. Turnbull C, Rapley EA, Seal S, et al: Variants near DMRT1, TERT and ATF7IP are associated with testicular germ cell cancer. Nat Genet 42:604-7, 2010

15. Kratz CP, Han SS, Rosenberg PS, et al: Variants in or near KITLG, BAK1, DMRT1, and TERT-CLPTM1L predispose to familial testicular germ cell tumour. J Med Genet 48:473-6, 2011

16. Rodriguez E, Houldsworth J, Reuter VE, et al: Molecular cytogenetic analysis of i(12p)-negative human male germ cell tumors. Genes Chromosomes Cancer 8:230-6, 1993

17. Samaniego F, Rodriguez E, Houldsworth J, et al: Cytogenetic and molecular analysis of human male germ cell tumors: chromosome 12 abnormalities and gene amplification. Genes Chromosomes Cancer 1:289-300, 1990

18. Rapley EA, Turnbull C, Al Olama AA, et al: A genome-wide association study of testicular germ cell tumor. Nat Genet 41:807-10, 2009

19. Sheikine Y, Genega E, Melamed J, et al: Molecular genetics of testicular germ cell tumors. Am J Cancer Res 2:153-67, 2012

20. Koul S, Houldsworth J, Mansukhani MM, et al: Characteristic promoter hypermethylation signatures in male germ cell tumors. Mol Cancer 1:8, 2002

21. Fitzmaurice C, Allen C, Barber RM, et al: Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol, 2016

22. Huyghe E, Matsuda T, Thonneau P: Increasing incidence of testicular cancer worldwide: a review. J Urol 170:5-11, 2003

23. McKiernan JM, Goluboff ET, Liberson GL, et al: Rising risk of testicular cancer by birth cohort in the United States from 1973 to 1995. J Urol 162:361-3, 1999

24. Zheng T, Holford TR, Ma Z, et al: Continuing increase in incidence of germ-cell testis cancer in young adults: experience from Connecticut, USA, 1935-1992. Int J Cancer 65:723-9, 1996

25. Bray F, Richiardi L, Ekbom A, et al: Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. Int J Cancer 118:3099-111, 2006

26. McGlynn KA, Devesa SS, Sigurdson AJ, et al: Trends in the incidence of testicular germ cell tumors in the United States. Cancer 97:63-70, 2003

27. Gajendran VK, Nguyen M, Ellison LM: Testicular cancer patterns in African-American men. Urology 66:602-5, 2005

28. Hemminki K, Li X: Familial risk in testicular cancer as a clue to a heritable and environmental aetiology. Br J Cancer 90:1765-70, 2004

29. Lip SZ, Murchison LE, Cullis PS, et al: A meta-analysis of the risk of boys with isolated cryptorchidism developing testicular cancer in later life. Arch Dis Child 98:20-6, 2013

30. Fossa SD, Chen J, Schonfeld SJ, et al: Risk of contralateral testicular cancer: a population-based study of 29,515 U.S. men. J Natl Cancer Inst 97:1056-66, 2005

31. Oliver RT, Mead GM, Rustin GJ, et al: Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol 29:957-62, 2011

32. Soper MS, Hastings JR, Cosmatos HA, et al: Observation versus adjuvant radiation or chemotherapy in the management of stage I seminoma: clinical outcomes and prognostic factors for relapse in a large US cohort. Am J Clin Oncol 37:356-9, 2014

33. Mortensen MS, Lauritsen J, Gundgaard MG, et al: A nationwide cohort study of stage I seminoma patients followed on a surveillance program. Eur Urol 66:1172-8, 2014

34. Tandstad T C-SE, Dahl O: Management of clinical stage I seminomatous testicular cancer: A report from SWENOTECA.

, American Society of Clinical Oncology, 2014

35. Kollmannsberger C, Tandstad T, Bedard PL, et al: Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. J Clin Oncol 33:51-7, 2015

36. Schmoll HJ, Jordan K, Huddart R, et al: Testicular non-seminoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20 Suppl 4:89-96, 2009

37. Albers P, Siener R, Krege S, et al: Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I Nonseminomatous testicular germ cell tumors: AUO trial AH 01/94 by the German Testicular Cancer Study Group. J Clin Oncol 26:2966-72, 2008

38. Westermann DH, Studer UE: High-risk clinical stage I nonseminomatous germ cell tumors: the case for chemotherapy. World J Urol 27:455-61, 2009

39. Oldenburg J, Fossa SD, Nuver J, et al: Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 24 Suppl 6:vi125-32, 2013

40. Hermans BP, Sweeney CJ, Foster RS, et al: Risk of systemic metastases in clinical stage I nonseminoma germ cell testis tumor managed by retroperitoneal lymph node dissection. J Urol 163:1721-4, 2000

41. Schmoll HJ, Jordan K, Huddart R, et al: Testicular seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 21 Suppl 5:v140-6, 2010

42. Domont J, Massard C, Patrikidou A, et al: A risk-adapted strategy of radiotherapy or cisplatin-based chemotherapy in stage II seminoma. Urol Oncol 31:697-705, 2013

43. De Santis M, Becherer A, Bokemeyer C, et al: 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. J Clin Oncol 22:1034-9, 2004

44. Donohue JP, Thornhill JA, Foster RS, et al: The role of retroperitoneal lymphadenectomy in clinical stage B testis cancer: the Indiana University experience (1965 to 1989). J Urol 153:85-9, 1995

45. Ehrlich Y, Brames MJ, Beck SD, et al: Long-term follow-up of Cisplatin combination chemotherapy in patients with disseminated nonseminomatous germ cell tumors: is a postchemotherapy retroperitoneal lymph node dissection needed after complete remission? J Clin Oncol 28:531-6, 2010

46. Oldenburg J, Alfsen GC, Lien HH, et al: Postchemotherapy retroperitoneal surgery remains necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses. J Clin Oncol 21:3310-7, 2003

47. Ravi P, Gray KP, O'Donnell EK, et al: A meta-analysis of patient outcomes with subcentimeter disease after chemotherapy for metastatic non-seminomatous germ cell tumor. Ann Oncol 25:331-8, 2014

48. Rosenberg B, Vancamp L, Krigas T: INHIBITION OF CELL DIVISION IN ESCHERICHIA COLI BY ELECTROLYSIS PRODUCTS FROM A PLATINUM ELECTRODE. Nature 205:698-9, 1965

49. de Wit R, Roberts JT, Wilkinson PM, et al: Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol 19:1629-40, 2001

50. Culine S, Kerbrat P, Kramar A, et al: Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Ann Oncol 18:917-24, 2007

51. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 15:594-603, 1997

52. de Wit R, Skoneczna I, Daugaard G, et al: Randomized phase III study comparing paclitaxel-bleomycin, etoposide, and cisplatin (BEP) to standard BEP in intermediate-prognosis germ-cell cancer: intergroup study EORTC 30983. J Clin Oncol 30:792-9, 2012

53. Nichols CR, Catalano PJ, Crawford ED, et al: Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 16:1287-93, 1998

54. Adra N, Ku K, Kalra M, et al: Survival outcomes of patients with metastatic germ cell tumor (mGCT) treated from 1998 to 2012: The Indiana University (IU) experience., J Clin Oncol 34, 2016 (suppl 2S; abstr 491)

55. Motzer RJ, Nichols CJ, Margolin KA, et al: Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. J Clin Oncol 25:247-56, 2007

56. Droz JP, Kramar A, Biron P, et al: Failure of high-dose cyclophosphamide and etoposide combined with double-dose cisplatin and bone marrow support in patients with high-volume metastatic nonseminomatous germ-cell tumours: mature results of a randomised trial. Eur Urol 51:739-46; discussion 747-8, 2007

57. Daugaard G, Skoneczna I, Aass N, et al: A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). Ann Oncol 22:1054-61, 2011

58. Fizazi K, Pagliaro L, Laplanche A, et al: Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. Lancet Oncol 15:1442-50, 2014

59. Adra N, Althouse SK, Liu H, et al: Prognostic factors in patients with poor-risk germ-cell tumors: a retrospective analysis of the Indiana University experience from 1990 to 2014. Ann Oncol 27:875-9, 2016

60. Albany CS, S; Brames, MJ; Suleiman, Y; Al Nasrallah, N; Perkins, S; Hanna, N; Einhorn, L: A retrospective analysis of patients with intermediate-risk germ cell tumor (IRGCT) treated at Indiana University from 2000 to 2010. J Clin Oncol 30, 2012 (suppl; abstr 4534), 2012

61. Fizazi KG, A; Mardiak, J: Mature results of the GETUG 13 phase III trial in poor-prognosis germ-cell tumors (GCT). J Clin Oncol 34, 2016 (suppl; abstr 4504), 2016

62. Feldman DR, Hu J, Dorff TB, et al: Paclitaxel, Ifosfamide, and Cisplatin Efficacy for First-Line Treatment of Patients With Intermediate- or Poor-Risk Germ Cell Tumors. J Clin Oncol 34:2478-83, 2016

63. Murphy BR, Breeden ES, Donohue JP, et al: Surgical salvage of chemorefractory germ cell tumors. J Clin Oncol 11:324-9, 1993

64. Kondagunta GV, Bacik J, Donadio A, et al: Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 23:6549-55, 2005

65. Loehrer PJ, Sr., Gonin R, Nichols CR, et al: Vinblastine plus ifosfamide plus cisplatin as initial salvage therapy in recurrent germ cell tumor. J Clin Oncol 16:2500-4, 1998

66. Loehrer PJ, Sr., Einhorn LH, Williams SD: VP-16 plus ifosfamide plus cisplatin as salvage therapy in refractory germ cell cancer. J Clin Oncol 4:528-36, 1986

67. Nichols CR, Tricot G, Williams SD, et al: Dose-intensive chemotherapy in refractory germ cell cancer--a phase I/II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation. J Clin Oncol 7:932-9, 1989

68. Einhorn LH, Williams SD, Chamness A, et al: High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med 357:340-8, 2007

69. Adra N, Abonour R, Althouse SK, et al: High-Dose Chemotherapy and Autologous Peripheral-Blood Stem-Cell Transplantation for Relapsed Metastatic Germ Cell Tumors: The Indiana University Experience. J Clin Oncol:Jco2016695395, 2016

70. Feldman DR, Sheinfeld J, Bajorin DF, et al: TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors: results and prognostic factor analysis. J Clin Oncol 28:1706-13, 2010

71. Feldman DV, M; Jia, X; Van Alstine, L; Patil, S; Fischer, P; Sheinfeld, J; Bosl, G; Motzer, R: Serum tumor marker (STM) decline rates during high-dose chemotherapy (HDCT) to predict outcome for germ cell tumor (GCT) patients (pts). J Clin Oncol 30, 2012 (suppl; abstr 4532)

72. Lorch A, Kleinhans A, Kramar A, et al: Sequential versus single high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: long-term results of a prospective randomized trial. J Clin Oncol 30:800-5, 2012

73. Pico JL, Rosti G, Kramar A, et al: A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. Ann Oncol 16:1152-9, 2005

74. Lorch A, Beyer J, Bascoul-Mollevi C, et al: Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. J Clin Oncol 28:4906-11, 2010

75. Kollmannsberger C, Pressler H, Mayer F, et al: Cisplatin-refractory, HER2/neu-expressing germ-cell cancer: induction of remission by the monoclonal antibody Trastuzumab. Ann Oncol 10:1393-4, 1999

76. Rick O, Braun T, Siegert W, et al: Activity of thalidomide in patients with platinum-refractory germ-cell tumours. Eur J Cancer 42:1775-9, 2006

77. Feldman DR, Turkula S, Ginsberg MS, et al: Phase II trial of sunitinib in patients with relapsed or refractory germ cell tumors. Invest New Drugs 28:523-8, 2010

78. Einhorn LH, Brames MJ, Heinrich MC, et al: Phase II study of imatinib mesylate in chemotherapy refractory germ cell tumors expressing KIT. Am J Clin Oncol 29:12-3, 2006

79. Adra NA, N; Radovich, M; Vaughn, D; Albany, C; Einhorn, L; Hanna, N: A phase II single arm multi-center trial evaluating the efficacy of pembrolizumab in the treatment of patients (pts) with incurable platinum refractory germ cell tumors (GCT), American Society of Clinical Oncology 2016

80. Taylor-Weiner A, Zack T, O'Donnell E, et al: Genomic evolution and chemoresistance in germ-cell tumours. Nature 540:114-118, 2016

81. Bagrodia A, Lee BH, Lee W, et al: Genetic Determinants of Cisplatin Resistance in Patients With Advanced Germ Cell Tumors. J Clin Oncol 34:4000-4007, 2016

82. van Walraven C, Fergusson D, Earle C, et al: Association of diagnostic radiation exposure and second abdominal-pelvic malignancies after testicular cancer. J Clin Oncol 29:2883-8, 2011

83. Travis LB, Fossa SD, Schonfeld SJ, et al: Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 97:1354-65, 2005

84. Travis LB, Beard C, Allan JM, et al: Testicular cancer survivorship: research strategies and recommendations. J Natl Cancer Inst 102:1114-30, 2010

85. Fung C, Fossa SD, Milano MT, et al: Solid tumors after chemotherapy or surgery for testicular nonseminoma: a population-based study. J Clin Oncol 31:3807-14, 2013

86. Houck W, Abonour R, Vance G, et al: Secondary leukemias in refractory germ cell tumor patients undergoing autologous stem-cell transplantation using high-dose etoposide. J Clin Oncol 22:2155-8, 2004

87. Kollmannsberger C, Hartmann JT, Kanz L, et al: Risk of secondary myeloid leukemia and myelodysplastic syndrome following standard-dose chemotherapy or high-dose chemotherapy with stem cell support in patients with potentially curable malignancies. J Cancer Res Clin Oncol 124:207-14, 1998

88. Abu Zaid MG-M, W; Williams, A: Metabolic syndrome (MetS) after platinum-based chemotherapy (CHEM): A multicenter study of North American testicular cancer survivors (TCS). J Clin Oncol 35, 2017 (suppl 5S; abstr 102), 2017

89. Haugnes HS, Wethal T, Aass N, et al: Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol 28:4649-57, 2010

90. Lampe H, Horwich A, Norman A, et al: Fertility after chemotherapy for testicular germ cell cancers. J Clin Oncol 15:239-45, 1997

91. Shinn EH, Swartz RJ, Thornton BB, et al: Testis cancer survivors' health behaviors: comparison with age-matched relative and demographically matched population controls. J Clin Oncol 28:2274-9, 2010

92. van den Belt-Dusebout AW, Nuver J, de Wit R, et al: Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 24:467-75, 2006

93. Willemse PM, Burggraaf J, Hamdy NA, et al: Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors. Br J Cancer 109:60-7, 2013

Table 1. Treatment Options for Clinical Stage I Testicular Cancer

Seminoma				
Option	**Outcomes**	**Pros**	**Cons**	**References**
Active Surveillance	20% relapse rate 99% cancer specific survival	Most men spared treatment Long-term outcomes are excellent even if patients relapse	Many physician visits Life disruption if relapse	Mortensen et al[33] Soper et al[32] Oldenburg et al[39]
Radiotherapy	4% relapse rate 99% cancer specific survival	Reduces risk for relapse Reduces risk for requiring chemotherapy Reduces frequency of abdominal imaging	Short-term side effects Long-term risk of secondary cancer	Soper et al[32] Oldenburg et al[39] Oliver et al[31]
Carboplatin (one or two cycles)	4% relapse rate 99% cancer specific survival	Reduces risk for relapse Reduces risk for requiring chemotherapy	Short-term side effects of carboplatin Long-term risks of carboplatin are unknown	Oldenburg et al[39] Oliver et al[31]
Non-seminoma				
Active Surveillance	30% relapse rate overall 15% relapse rate if no risk factors 50% relapse rate in high-risk group with risk facors 99% cancer specific survival	Most men spared treatment Long-term outcomes are excellent even if patients relapse	Many physician visits Life disruption if relapse	Kollmannsberger et al[35] Schmoll et al[36] Tandstad et al[34]
Retroperitoneal Lymph Node Dissection	20-30% relapse rate 99% cancer specific survival	Cures some patients with pathologic stage II disease Avoid the need for chemotherapy in some patients	Surgical risk Most patients will have normal pathology in retroperitoneal lymph nodes	Schmoll et al[36] Albers et al[37]

		Disease does not recur in the retroperitoneum	Chemotherapy might be required if patients relapse	
Bleomycin, Etoposide, Cisplatin (1 cycle)	1-5% relapse rate 99% cancer specific survival	Reduces risk patients will require longer course of chemotherapy	Early toxicity Overtreatment in substantial number of patients Long-term risk of 1 or 2 cycles of chemotherapy is unknown	Schmoll et al[36] Tandstad et al[34] Albers et al[37] Westermann et al[38]

Table 2. Treatment of Clinical Stage II Testicular Cancer

Seminoma			
Option	**Indication**	**Outcomes**	**References**
Radiotherapy 30-36 Gy to para-aortic and ipsilateral iliac lymph nodes	Non-bulky disease (<3cm)	5 year overall survival 97%	Domont et al[42] Schmoll et al[41]
Chemotherapy BEPx3 or EPx4	Bulky disease (>3cm)	5 year overall survival 98%	Domont et al[42] Schmoll et al[41]
Non-seminoma			
Retropertioneal Lymph Node Dissection	Non-bulky disease (<3cm)	5 year overall survival 98%	Donohue et al[44] Schmoll et al[36]
Chemotherapy BEP x 3 or EP x4	Bulky disease (>3cm)	5 year overall survival 98%	Schmoll et al[36]
	Abbreviations: BEP, bleomycin-etoposide-cisplatin; EP, etoposide-cisplatin		

Table 3. First-line Treatment of Stage III Testicular Cancer

Treatment	Indication	Outcomes	References
Good Risk Disease* Seminoma: any primary tumor site + no NPVM + any tumor marker levels (hCG, LDH) Non-seminoma: testis or retroperitoneal primary + no NPVM + good tumor marker levels (AFP < 1,000 ng/mL, hCG < 5,000 mIu/mL, LDH < 1.5 x upper limit of normal)			
BEPx3 EPx4	For most patients Patients to avoid bleomycin (age>50, serum Cr>2)	5 year PFS 90% 5 year OS 97%	Bosl et al[3] Williams et al[6] Einhorn et al[5] de Wit et al[49] Culine et al[50]
Intermediate Risk* Seminoma: any primary tumor site + NPVM + any tumor marker level (hCG, LDH) Non-seminoma: testis or retroperitoneal primary + no NPVM + intermediate tumor marker levels (AFP 1,000-10,000 ng/mL, hCG 5,000-50,000 mIu/mL, LDH 1.5-10 x upper limit of normal)			
BEPx4 or VIPx4 BEPx3 + EPx1	For intermediate risk patients with high tumor bulk For low volume intermediate risk patients	5 year PFS 84% 5 year OS 93%	de Wit et al[52] Nichols et al[53] Albany et al[60]
Poor Risk Disease* Seminoma: none are poor risk Non-seminoma: Mediastinal primary OR NPVM OR poor tumor marker levels (AFP > 10,000 ng/mL, hCG > 50,000 mIu/mL, LDH > 10 x upper limit of normal)			
BEPx4 or VIPx4	For all patients	5 year PFS 58% 5 year OS 73%	Nichols et al[53] Motzer et al[55] Droz et al[56] Daugaard et al[57] Fizazi et al[58] Adra et al[59]
Abbreviations: NPVM, non-pulmonary visceral metastasis; BEP, bleomycin-etoposide-cisplatin; EP, etoposide-cisplatin; PFS, progression-free survival; OS, overall survival ; Cr, creatinine *Risk per IGCCCG (International Germ Cell Cancer Collaborative Group)			